

## Current Literature

In Clinical Science



## Trigeminal Nerve Stimulation May Not Be Effective for the Treatment of Refractory Partial Seizures

### Randomized Controlled Trial of Trigeminal Nerve Stimulation for Drug-Resistant Epilepsy.

DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, Oviedo S, Gordon S, Corralle-Leyva G, Kealey CP, Heck CN. *Neurology* 2013;80:786–791.

**OBJECTIVE:** To explore the safety and efficacy of external trigeminal nerve stimulation (eTNS) in patients with drug-resistant epilepsy (DRE) using a double-blind randomized controlled trial design, and to test the suitability of treatment and control parameters in preparation for a phase III multicenter clinical trial. **METHODS:** This is a double-blind randomized active-control trial in DRE. Fifty subjects with 2 or more partial onset seizures per month (complex partial or tonic-clonic) entered a 6-week baseline period, and then were evaluated at 6, 12, and 18 weeks during the acute treatment period. Subjects were randomized to treatment (eTNS 120 Hz) or control (eTNS 2 Hz) parameters. **RESULTS:** At entry, subjects were highly drug-resistant, averaging 8.7 seizures per month (treatment group) and 4.8 seizures per month (active controls). On average, subjects failed 3.35 antiepileptic drugs prior to enrollment, with an average duration of epilepsy of 21.5 years (treatment group) and 23.7 years (active control group), respectively. eTNS was well-tolerated. Side effects included anxiety (4%), headache (4%), and skin irritation (14%). The responder rate, defined as >50% reduction in seizure frequency, was 30.2% for the treatment group vs 21.1% for the active control group for the 18-week treatment period (not significant,  $p = 0.31$ , generalized estimating equation [GEE] model). The treatment group experienced a significant within-group improvement in responder rate over the 18-week treatment period (from 17.8% at 6 weeks to 40.5% at 18 weeks,  $p = 0.01$ , GEE). Subjects in the treatment group were more likely to respond than patients randomized to control (odds ratio 1.73, confidence interval 0.59-0.51). eTNS was associated with reductions in seizure frequency as measured by the response ratio ( $p = 0.04$ , analysis of variance [ANOVA]), and improvements in mood on the Beck Depression Inventory ( $p = 0.02$ , ANOVA). **CONCLUSIONS:** This study provides preliminary evidence that eTNS is safe and may be effective in subjects with DRE. Side effects were primarily limited to anxiety, headache, and skin irritation. These results will serve as a basis to inform and power a larger multicenter phase III clinical trial. **CLASSIFICATION OF EVIDENCE:** This phase II study provides Class II evidence that trigeminal nerve stimulation may be safe and effective in reducing seizures in people with DRE.

### Commentary

Stimulatory devices offer a novel approach for the treatment of refractory partial seizures. Both peripheral and central stimulatory devices that provide either continuous or responsive stimulation have been studied. Currently the only approved device is the vagus nerve stimulator (VNS). Stimulatory devices may provide a safe and well-tolerated means of reducing seizures for patients with refractory seizures.

Trigeminal nerve stimulation (TNS) is a neuromodulatory device that has been studied in animal and pilot clinical trials. The original article investigating its potential antiepileptic properties was an animal study evaluating its effect on pentylenetetrazole-induced seizure activity in awake rats (1). Continuous unilateral stimulation of the trigeminal nerve re-

duced electrographic seizure severity and duration activity in a frequency-dependent fashion at frequencies >100 Hz. Bilateral trigeminal stimulation was more effective than unilateral stimulation. A proof-of-concept clinical trial investigated safety and efficacy among seven subjects using transcutaneous stimulation of the infraorbital and supraorbital branches of the trigeminal nerve (2). In this study, TNS was well tolerated, and four of seven subjects who completed  $\geq 3$  months had a  $\geq 50\%$  reduction in seizure frequency. Another study evaluated its effect in depression and found significant improvement in clinician- and individual-rated depression scales among five subjects (3). There has not previously been a randomized, blinded, controlled trial among persons with refractory epilepsy.

DeGiorgio and colleagues completed a phase-2 randomized, double-blind, multicenter trial evaluating external TNS (eTNS) among subjects with drug-resistant partial-onset epilepsy (having two or more complex partial or generalized tonic seizures per month for 2 consecutive months) (4). Subjects were randomized to either active treatment (frequency of 120

*Epilepsy Currents*, Vol. 13, No. 4 (July/August) 2013 pp. 164–165  
© American Epilepsy Society

OPEN ACCESS Freely available online



Hz and pulse duration <250  $\mu$ s) or control parameters (frequency, 2 Hz; duty cycle, 2 seconds on and 90 seconds off; and pulse duration, 50  $\mu$ s). The active settings were derived from results from both the animal study in a pentylentetrazole model of epilepsy as well as the open-label proof-of-concept study. The control parameters were extrapolated from settings used in VNS trials. A novel bipolar transcutaneous gel-based electrode, specifically designed to contact the right and left branches of the ophthalmic and supratrochlear nerves to provide bilateral stimulation, was utilized. Subjects were enrolled at the University of Southern California (USC) and the University of California–Los Angeles (UCLA) using block randomization. After completing a 6-week baseline period, subjects were evaluated at 6, 12, and 18 weeks.

Three primary endpoints were defined: 1) change in seizure frequency, 2) responder rate defined as  $\geq 50\%$  reduction in seizure frequency, and 3) time to fourth seizure. Because there were three primary outcomes, a Bonferroni correction was utilized giving a significance level of  $p = 0.0167$  ( $0.05/3$ ). Secondary measures included mood as measured by Beck Depression Index and response ratio.

Overall, subjects had refractory epilepsy with an average of 8.7 seizures per month and had failed an average of 3.35 antiepileptic drugs (AEDs) prior to enrollment. As in prior studies (2, 3), eTNS was well tolerated, with the most common reported side effect being skin irritation (14%) followed by anxiety (4%) and headache (4%).

There were no significant differences between the active group and control group in any of the three predefined primary end points. There was, however, a significant within-group difference improvement in responder rate over the 18-week treatment period. At 6 weeks, the responder rate was 17.8%, which then increased to 40.5% at 18 weeks, giving a significant within-group improvement ( $p = 0.01$ ). It is, however, unclear how the responder rates at the serial evaluation periods were derived. The reported percentages could reflect a cumulative response between the different evaluation periods or may have reflected a more limited time period. The secondary outcome, response ratio, was also not significantly

different between the active and control groups. Similar to the responder rate, there was a significant within-group difference ( $p < 0.04$ ). Mood was improved with eTNS treatment compared with control (within- and between-group differences,  $p < 0.02$ ).

Although interesting, these data do not support the effectiveness of eTNS for the treatment of refractory partial seizures. The device was well tolerated with minimal side effects. As no predefined primary end point was met, it is unclear how as suggested in the manuscript, this study provides preliminary evidence that eTNS may be effective as treatment for refractory partial seizures. In addition, although the study was designed to provide class II evidence for the safety and efficacy of eTNS as therapy for partial seizures, this evidence was not found in this study because of the lack of significant findings in any of the primary end points. Of interest, depression did improve with eTNS. Future larger scale trials with larger sample sizes may provide evidence to support the effectiveness of trigeminal nerve stimulation for the treatment of refractory partial seizures. Future trials evaluating the effectiveness of trigeminal nerve stimulation for the treatment of depression should also be considered.

by Alison M. Pack, MD, MPH

#### References

1. Fanselow EE, Reid AP, Nicoletis MA. Reduction of pentylentetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci* 2000;20:8160–8168.
2. DeGiorgio CM, Shewmon A, Murray D, Whitehurst T. Pilot study of trigeminal nerve stimulation (TNS) for epilepsy: A proof-of-concept trial. *Epilepsia* 2006;47:1213–1215.
3. Schrader LM, Cook IA, Miller PR, Maremont ER, DeGiorgio CM. Trigeminal nerve stimulation in major depressive disorder: First proof of concept in an open pilot trial. *Epilepsy Behav* 2011;22:475–478.
4. DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, Oviedo S, Gordon S, Corralle-Leyva G, Kealey CP, Heck CN. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology* 2013;80:786–791.



# American Epilepsy Society

## *Epilepsy Currents Journal*

### Disclosure of Potential Conflicts of Interest

#### **Instructions**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### **1. Identifying information.**

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

#### **2. The work under consideration for publication.**

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### **3. Relevant financial activities outside the submitted work.**

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Other relationships**

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



# American Epilepsy Society

## Epilepsy Currents Journal

### Disclosure of Potential Conflicts of Interest

#### Section #1 Identifying Information

1. Today's Date: May 7, 2012
2. First Name Alison Last Name Pack Degree MD, MPH
3. Are you the Main Assigned Author?  Yes  No

If no, enter your name as co-author:

4. Manuscript/Article Title: Trigeminal Nerve Stimulation May Not Be Effective for the Treatment of Refractory Partial Seizures
5. Journal Issue you are submitting for: 13.4

#### Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>				
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input type="checkbox"/>		NIH		
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>				
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input type="checkbox"/>	X		Vivus	Paid for flight and hotel to meeting
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>				

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest.

Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.  
Epilepsy Currents Editorial Board